The Examiner's outstanding rejections of the claims and specification are addressed in turn below. The instant amendments, arguments, and response are believed to place the application in condition for allowance. If for any reason the Examiner finds the Amendment and Response to be insufficient in any way, or identifies any other outstanding issue, the Examiner is urged to call the undersigned Attorney to address the perceived insufficiency or issue in order to expedite prosecution of the case.

Rejection of the claims under 35 U.S.C. § 112, ¶ 1

The specification is objected to, and claims 2-4 stand rejected, under section 112, first paragraph, for allegedly failing to teach adequately how to make and/or use the invention. The Examiner maintains that the specification does not provide enablement for a device comprising osteogenic protein wherein said protein is an amino acid sequence variant of the recited osteogenic proteins or wherein the osteogenic protein comprises an amino acid sequence having at least 70% sequence homology with the C-terminal 102-106 amino acids, including the conserved seven cysteine domain, of human OP-1 without regard to the functional activity of the osteogenic protein. Applicants respectfully traverse the rejection to the extent that it is maintained over the claims as amended and the arguments set forth below.

Claims 2-4 have been amended to recite that the amino acid sequence variants for use in the invention have substantially similar osteogenic activity as the enumerated osteogenic proteins. Furthermore, claim 1 (from which claims 2-4 each depend) has been amended to recite that osteogenic proteins for use in the invention include those proteins capable of inducing repair of endochondral bone, or cartilage, chondral, or osteochondral defects. The specification provides specific guidance in identifying those proteins capable of inducing repair of endochondral bone, or cartilage, chondral, or osteochondral defects through an assay designed to measure all the critical events associated with endochondral bone morphogenesis (see page 56, line 1 through page 57, line 24, as well as the references cited and incorporated by reference

[redacted]

thereon). Applicants submit therefore that the specification provides adequate guidance to permit one of skill in the art to practice the invention as claimed in claims 2-4, as amended.

Section 112, first paragraph, requires that Applicants teach how to make, use and test the claimed invention in sufficient detail to permit the skilled artisan to practice the subject matter of claims 2-4, as amended, with a reasonable expectation of success. Applicants respectfully submit that the instant specification complies with this legal standard. The rejection of claims 2-4 under section 112, first paragraph, should be withdrawn in light of the amendments to the claims and the arguments presented herein.

Rejection of the claims under 35 U.S.C. § 102

Claims 1, 7-15 and 20-24 currently stand rejected as being anticipated under 35 U.S.C. § 102(b). Claims 1, 7-15, 20-22 and 24 are rejected as anticipated by Amman, *et al.*, U.S. Patent No. 5,422,340 (hereinafter "Amman"). Claims 23 and 24 are rejected as anticipated under 35 U.S.C. § 102(b) by Lindstrom, *et al.*, U.S. Patent No. 5,366,964 (hereinafter "Lindstrom"). Finally, claims 1-4 currently stand rejected under 35 U.S.C. § 102(e) as being anticipated by Kuberasampath, *et al.*, U.S. Patent No. 5,645,591 (hereinafter "Kuberasampath I"). Applicants respectfully traverse these rejections to the extent they are maintained over the claim amendments and arguments presented herein.

In order for a prior art reference to anticipate under 35 U.S.C. § 102, all elements of the claim must be found in a single piece of prior art. In re Bond, 910 F.2d 831, 15 U.S.P.Q.2d 1566 (Fed. Cir. 1990). Applicants respectfully submit that none of the cited reference identically discloses all elements of the claims, as amended.

Rejections under Section 102(b)

Rejection over Amman

The Examiner rejects claims 1, 7-15, 20-22 and 24 under 35 U.S.C. § 102(b) as being anticipated by Amman, because Amman discloses a composition comprising an osteogenic protein, wherein the osteogenic protein is TGF-β. Claims 1 and 20 have been amended to recite the element of an osteogenic proteins capable of inducing repair of endochondral bone, or cartilage, chondral, or osteochondral defects. Amman, however, only teaches the use of TGF-β. As noted in the Amendment filed May 11, 1998 (Paper No. 8), the protein TGF-β is not capable of inducing local endochondral bone or cartilage formation. In Paper No. 8, Applicants directed the Examiner's attention to the article Beck, *et al.*, (1991), J. Bone and Min. Res. 6:1257-1265 at p. 1264. The authors of the Beck article note that TGF-β results in bone formation without cartilaginous intermediates, *i.e.,* non-endochondral bone, whereas bone morphogenic proteins (hereinafter "BMPs") or "osteogenic proteins" induce bone formation with a cartilaginous intermediate, *i.e.,* endochondral bone. This is a fundamental difference between TGF-β and Applicants' BMPs as contemplated by the claims.

Applicants submit, therefore, that Amman does not teach the use of an osteogenic protein capable of inducing repair of endochondral bone, or cartilage, chondral, or osteochondral defects in conjunction with a matrix and binding agent as recited in claims 1 and 20, as amended. Since Amman does not teach the element of an osteogenic protein capable of inducing local endochondral bone or cartilage formation, it does not contain all of the elements of claims 1 and 20, as amended, and it therefore does not anticipate claims 1 and 20, as amended, under 35 U.S.C. § 102(b). Applicants submit therefore that claims 1 and 20, as amended, are allowable under 35 U.S.C. § 102(b) over Amman, and that claims 7-15, 21, 22 and 24 are also allowable as depending from now allowable base claims.

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Rejection over Lindstrom

The Examiner rejects claims 23 and 24 under 35 U.S.C. § 102(b) as being anticipated by Lindstrom, because Lindstrom discloses a composition comprising an osteogenic protein, wherein the osteogenic protein is TGF-β. Claim 23 has been amended to recite an osteogenic protein capable of inducing repair of endochondral bone, or cartilage, chondral, or osteochondral defects. As noted above in connection with the rejection over Amman, TGF-β does not fall within the scope of those osteogenic proteins capable of inducing repair of endochondral bone, or cartilage, chondral, or osteochondral defects. As such, the fundamental element of an osteogenic protein capable of inducing repair of endochondral bone, or cartilage, chondral, or osteochondral defects, is not included in the Lindstrom reference. Applicants submit therefore that claim 23, as amended, is allowable under 35 U.S.C. § 102(b) over Lindstrom. Applicants further submit that claim 24 is also allowable under 35 U.S.C. § 102(b) as depending from a now allowable base claim.

Rejection under Section 102(e)

The Examiner rejects claims 1-4 under 35 U.S.C. § 102(e) as being anticipated by Kuberasampath I, because Kuberasampath I allegedly discloses a device comprising osteogenic protein, a matrix derived from a non-synthetic, non-polymeric material other than demineralized bone, and a binding agent. This rejection is traversed to the extent it is maintained over the claims as amended and the arguments presented herein.

Claim 1 has been amended to recite a "non-synthetic, non-polymeric matrix other than demineralized bone." Kuberasampath I discloses a device comprising a synthetic, polymeric matrix derived from collagen and glycosaminoglycan. Kuberasampath I does not, however, disclose a device comprising a non-synthetic, non-polymeric matrix other than demineralized bone, as is claimed in claim 1, as amended. Applicants submit therefore that Kuberasampath I

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does not anticipate claim 1, as amended, and that claim 1, as amended, is allowable under 35 U.S.C. § 102(e) over Kuberasampath I. Furthermore, Applicants submit that claims 2-4 are also allowable as now depending from an allowable base claim.

Rejection of the claims under 35 U.S.C. § 103(a)

Claims are also rejected as being unpatentable under 35 U.S.C. § 103(a). Claims 1 and 9 are rejected as being unpatentable over Amman in view of LeGeros, *et al.*, II CRC Handbook of Bioactive Ceramics (CRC Press), pp. 17-28 (1990) (hereinafter "LeGeros"). Claims 1, 20-22, 32 and 33 are rejected as being unpatentable over Amman. Claims 23, 24, and 26-30 are rejected as being unpatentable over Lindstrom. Claims 1, 5, 17-19 and 26-31 are rejected as being unpatentable over Cook, *et al.*, (1994) J. Bone and Joint Surg., 76-A(6):827-38 (hereinafter "Cook") in view of O'Leary, *et al.*, U.S. Patent No. 5,073,373 (hereinafter "O'Leary"). Claims 1, 15-19 and 25 are rejected as unpatentable over Cook, in view of O'Leary and further in view of Kuberasampath, *et al.*, U.S. Patent No. 5,171,574 (hereinafter "Kuberasampath II"). Finally, claims 1 and 6 are rejected as unpatentable over Kuberasampath I in view of Ogawa, *et al.*, (1992) J. Biol. Chem. 267:1423-7 (hereinafter "Ogawa"). These rejections are traversed to the extent they are maintained over the claims as amended and the arguments presented herein.

Rejection of claims 1 and 9

The Examiner rejects claims 1 and 9 as being unpatentable under 35 U.S.C. § 103(a) over Amman in view of LeGeros, because LeGeros teaches the use of a combination of hydroxyapatite (HA) and tricalcium phosphate (TCP) as a matrix and Amman teaches a composition comprising TGF-β, matrix, and binder. The Examiner asserts that it would have been obvious to one of ordinary skill in the art to combine the composition of Amman with the teachings of LeGeros to make a composition comprising HA, TCP, and an osteogenic protein.

Applicants respectfully submit that the combination of elements comprising the invention defined by Applicants' claims, as amended, is neither taught nor suggested by either of the cited references taken singly or combined. Claim 1, as amended, defines a device comprising osteogenic protein capable of inducing repair of endochondral bone, or cartilage, chondral, or osteochondral defects, non-synthetic, non-polymeric matrix other than demineralized bone, and binding agent. Claim 9 defines this device with at least two different matrices. Amman teaches the use of TGF-β, but, as discussed above in connection with the rejection of claims 1, 7-15, 20-22, and 24 under 35 U.S.C. § 102(b), TGF-β is not an osteogenic protein capable of inducing repair of endochondral bone, or cartilage, chondral, or osteochondral defects. Amman does not, therefore, teach the use of an osteogenic protein capable of inducing repair of endochondral bone, or cartilage, chondral, or osteochondral defects as claimed in claim 1, as amended. LeGeros also does not teach or suggest the use of an osteogenic protein as claimed. Since neither reference taken singly or combined recites all of the elements of claim 1, as amended, or the elements of claim 9 (which depends from claim 1), they cannot support a rejection of these claims under 35 U.S.C. § 103(a).

Rejection of claims 1, 20-22, 32 and 33

The Examiner rejects claims 1, 20-22, 32 and 33 as being unpatentable under 35 U.S.C. § 103(a) over Amman, because Amman teaches a composition comprising TGF-β, matrix, and binder. The Examiner further asserts that it would have been obvious to one of ordinary skill in the art to combine the composition of Amman in a kit.

Claims 1 and 20 have been amended to recite an osteogenic protein capable of inducing repair of endochondral bone, or cartilage, chondral, or osteochondral defects. Again, Applicants respectfully submit that Amman does not teach or suggest the use of an osteogenic protein capable of inducing repair of endochondral bone, or cartilage, chondral, or osteochondral defects as claimed in claims 1 and 20, as amended. Since the element of an osteogenic protein capable

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of inducing repair of endochondral bone, or cartilage, chondral, or osteochondral defects is not present in Amman, it cannot support a rejection of claims 1, 20-22, 32 and 33 under 35 U.S.C. § 103(a).

Rejection of claims 23, 24 and 26-30

The Examiner rejects claims 23, 24 and 26-30 as being unpatentable under 35 U.S.C. § 103(a) over Lindstrom, because Lindstrom teaches a composition comprising TGF-β, 0.01%-10% binding agent, and 0.1 ng/ml-1 g/ml matrix for use in orthopedic applications. The Examiner asserts that it would have been obvious to one of ordinary skill in the art to use the composition of Lindstrom to heal bone.

Applicants respectfully submit that Lindstrom does not teach or suggest all of the elements of the claims. Claims 23 and 26 have been amended to recite an osteogenic protein capable of inducing repair of endochondral bone, or cartilage, chondral, or osteochondral defects. Lindstrom only teaches the use of TGF-β. Lindstrom therefore does not teach or suggest the use of an osteogenic protein capable of inducing repair of endochondral bone, or cartilage, chondral, or osteochondral defects as claimed in claims 23 and 26, as amended. Since the element of an osteogenic protein capable of inducing repair of endochondral bone, or cartilage, chondral, or osteochondral defects is not present in Lindstrom, it cannot support a rejection of claims 23, 24, and 26-30 under 35 U.S.C. § 103(a).

Rejection of claims 1, 5, 17-19 and 26-31

The Examiner rejects claims 1, 5, 17-19 and 26-31 as being unpatentable under 35 U.S.C. § 103(a) over Cook in view of O'Leary. The Examiner asserts that Cook teaches a composition comprising BMP and collagen for bone formation. The Examiner then asserts that O'Leary teaches a composition comprising carboxymethylcellulose (hereinafter "CMC") and that O'Leary teaches that CMC improves the ability of the composition to keep the bone powder in

suspension. The Examiner asserts that it would have been obvious to one of ordinary skill in the art to combine the composition of Cook with the teachings of O'Leary to improve the ability of the composition to keep collagen in suspension and make application of a homogeneous composition easier.

Applicants respectfully submit that the above-cited references cannot be combined to support a rejection under 35 U.S.C. § 103(a), because there is no motivation to combine their individual teachings. The secondary reference, O'Leary, teaches a composition comprising preferably a matrix, such as demineralized bone, and preferably a liquid carrier, such as glycerol. With respect to this basic composition, O'Leary notes in col. 3, l. 62-64 that "bone powder has a tendency to quickly or prematurely separate from the carrier or to otherwise settle out from the composition." In order to address the problem of the bone powder separating from the liquid carrier (*i.e.*, glycerol), O'Leary teaches that a "thickener," such as CMC or collagen, may be added to the basic composition. O'Leary does not require CMC, as do Applicants, and O'Leary does not teach or suggest that CMC would be useful with a matrix other than demineralized bone. Furthermore, and important to this analysis, O'Leary teaches that collagen can be used as an alternative to CMC, therefore indicating that O'Leary never contemplated using collagen and CMC together. In contrast, Applicants require both.

Cook teaches a composition comprising only collagen and OP1 for bone formation. Cook does not discuss the handling characteristics or homogeneity of the composition, and therefore does not teach or suggest that a "thickener" may be added to the composition to improve these characteristics. Thus, Cook does not teach or suggest that a problem exists with the consistency or handling characteristics of a collagen and OP1 containing composition. One of ordinary skill in the art relying on Cook would therefore not be motivated to modify a collagen and OP1 containing composition.

The present invention is directed to a composition comprising osteogenic protein, such as OP1, non-synthetic, non-polymeric matrix other than demineralized bone, such as collagen, and binding agent, such as CMC. As noted at p. 3, l. 17 of the instant specification, compositions of collagen and osteogenic protein, such as those described in Cook, "have a dry, sandy consistency." The addition of binding agent (*i.e.*, CMC) to a composition comprising collagen and osteogenic protein would therefore not be made to address the problem of matrix "quickly or permanently separating" from a carrier, as taught by O'Leary.

One of ordinary skill in the art reading Cook and O'Leary would, therefore, not be motivated to combine the teachings of the two references, because O'Leary teaches a combination of materials that address a problem specific to using demineralized bone as a matrix in a liquid carrier. One of ordinary skill in the art relying on O'Leary would only be motivated to add CMC to a composition that does not contain collagen or a composition in which a matrix in a liquid would not form a suspension, a problem which seems to be unique to demineralized bone. O'Leary does not teach or suggest that the addition of a "thickener" (*i.e.*, CMC) is necessary to improve the homogeneity of a composition comprising collagen and osteogenic protein. Finally, one of ordinary skill in the art reading Cook and O'Leary would not be motivated to combine the teachings of the two references, because Cook does not teach or suggest that there is a problem with the consistency or handling characteristics of a collagen and OP1 containing composition. One of ordinary skill in the art relying on Cook would, therefore, not be motivated to modify such a composition.

Applicants submit, therefore, that one of ordinary skill in the art reading Cook and O'Leary would not be motivated to combine the two references to make a composition comprising osteogenic protein, non-synthetic, non-polymeric matrix other than demineralized bone, and binding agent, as in claim 1, as amended. Furthermore, one of ordinary skill in the art relying on Cook and O'Leary would not be motivated to make a device comprising OP1,

collagen matrix, and CMC, as in claims 17 and 31. Since one of ordinary skill in the art reading O'Leary would not be motivated to make a composition according to claim 1, as amended, and to claims 17 and 31, O'Leary cannot be combined with Cook to support a rejection of those claims under 35 U.S.C. § 103(a). Finally, Applicants submit that claims 5, 18, 19, and 26-30 are also allowable as depending from allowable base claims.

Rejection of claims 1, 15-19 and 25

The Examiner rejects claims 1, 15-19, and 25 as being unpatentable under 35 U.S.C. § 103(a) over Cook in view of O'Leary, as described above, and further in view of Kuberasampath II. The Examiner asserts that it would have been obvious to one of skill in the art to combine Cook and O'Leary, as described above, to obtain the device of claims 1, 15-19, and 25 by adding saline, as taught by Kuberasampath II.

As discussed above, Applicants submit that claim 1, as amended, and claim 17 are patentable under 35 U.S.C. § 103(a) over Cook in view of O'Leary, because there is no motivation to combine the teachings of Cook with O'Leary to make the invention of claim 1, as amended, and claim 17. Applicants submit that claims 15, 18, 19, and 25 are also allowable under 35 U.S.C. § 103(a) as depending from allowable base claims 1 and 17.

Rejection of claims 1 and 6

The Examiner rejects claims 1 and 6 as being unpatentable under 35 U.S.C. § 103(a) over Kuberasampath I in view of Ogawa, because it would be obvious to one of ordinary skill in the art to modify the teaching of Kuberasampath I to include two different osteogenic proteins, as taught by Ogawa. The rejection is traversed to the extent it is maintained over the amendments to the claims and the arguments presented herein.

As noted above with respect to the rejection of claims 1-4 under 35 U.S.C. § 102(e) over Kuberasampath I, Kuberasampath I does not teach the element of a non-synthetic, non-polymeric matrix derived from a material other than demineralized bone. Kuberasampath I does not, therefore, teach all of the elements of claim 1, as amended. Furthermore, Ogawa does not teach the combination of two or more osteogenic proteins capable of inducing local endochondral bone or cartilage formation as is claimed in claim 1, as amended. Since neither reference taken singly or combined teaches all of the elements of claim 1, as amended, and claim 6 (which depends from claim 1), they cannot support a rejection of claim 1 under 35 U.S.C. § 103(a).

Claims 35 and 36

In the final Office Action mailed from the Patent Office on August 4, 1998, the Examiner neither allowed nor rejected claims 35 and 36. Applicants submit that these claims are allowable as depending from now allowable base claims.

CONCLUSION

In view of the arguments set forth above and the claim amendments presented herein, Applicants respectfully submit that the pending claims as amended are in condition for immediate allowance. Reconsideration respectfully is requested. The Examiner is urged to contact the undersigned to discuss the amendment and/or remarks presented herein.

Respectfully submitted,

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